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WARTIME RESPONSIBILITIES OF THE UNITED STATES PUBLIC HEALTH SERVICE*

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229
43

THE recent trend of events in the war has been encouraging. The fight, however, is still far from won. For years the United States Public Health Service has had its own battle to wage—a battle against death, disease and suffering. Our job is pretty much the same in war or peace. It is heightened, of course, and brought into sharper focus by the exigencies of war; but our function remains always clearly and simply one of maintaining the Nation's health—by "holding the line against preventable disease."

The first eighteen months of war have given the federal health authorities an opportunity to evaluate their health-protection measures and to clarify those problems most likely to need wartime amplification. The health of the Nation, as measured by death rates and the incidence of communicable diseases, remained good during 1942. Provisional data indicate that the general death rate for 1942 is the lowest ever recorded, 10.3 per 1000 population, as compared to 10.5 for 1941. The increase of fatal accidents in industry almost offset the reduction in deaths from automobile accidents.

One of our functions is the prompt control of epidemic diseases, a threat to the war effort. There have been substantial increases in two epidemic diseases and the outbreak of a new infection among war workers.

Meningococcal meningitis, also known as cerebrospinal fever, caused much loss of life in the last war. In 1942 the incidence of the disease was well above the expected level. This year to date over twice as many cases were reported as for all of last year. The final figures for 1943 will probably show the greatest rise in meningococcal meningitis since 1913. Yet the situation today is much more hopeful than it was twenty-five years ago, when there was no satisfactory treatment. It has been found, for instance, that prompt administration of sulfonamide drugs will save a great majority of patients and is more effective than the combination of drugs and serum. In some reports to the Public Health Service, the fatality rate has been as low as 5 per cent.

Endemic typhus fever, which increased in 1942, has shown a continuing rise throughout 1943. A year ago an Office of Typhus Fever Control was established with headquarters at Atlanta, Georgia, to assist threatened communities in combating this rise. Surveys of rat harborages are made by this office, buildings are rat-proofed, and rats are destroyed. The Public Health Service also assists the Army in the rodent control of military establishments. In addition, we have been carrying on typhus research for a number of years. One of our officers has developed a vaccine believed to be the most effective of any known for the prevention of typhus. Experiments in the production of lice repellents are also encouraging.

Late in 1941, an epidemic eye infection, known as keratoconjunctivitis, appeared in the shipyards of the West Coast and spread through war industries there, and has since attacked numerous industrial groups in other sections of the country. The probable cause of the disease is a virus. It is not a fatal infection, but disables workers for from two to eight weeks and occasionally impairs vision through injury to the cornea. The Public Health Service has widely publicized the conditions among professional workers in state and local governments, the medical field and private industry. Recommendations for the control of this disease have been made. There is, however, no specific cure.

The Public Health Service quarantine authorities are on hand wherever necessary to guard the home front. The great impetus of air traffic—the increased speed of travel—has made it possible for a person to contract any of the quarantinable or

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tropical diseases in distant parts of the world and to reach the United States before the condition has become manifest. Commercial and military aircraft are now examined by medical officers for the presence of disease, passengers are kept under surveillance, and planes are disinsecticized. Ships touching our ports are inspected for infestation by rats. New ships constructed for the wartime merchant marine incorporate the Public Health Service rat-proofing specifications.

Although reports of infectious diseases from enemy-occupied countries are incomplete, the Public Health Service keeps tabs on the world-wide incidence of disease. We have knowledge of thousands of cases of typhus throughout Europe and Africa. Recent reports show that gastroenteritis, tuberculosis, typhoid fever and trachoma are prevalent in North Africa, and malaria in Morocco and Egypt.

The problem of returning troops infected with various tropical diseases has been studied by the Public Health Service, the Army, the Navy and the National Research Council. These diseases include filariasis, a disease of the lymph nodes for which there is no preventive treatment and no sure cure, and schistosomiasis, also a stubborn long-term disease. The means of transmission in other countries is known, and the Division of Zoölogy of the National Institute of Health is making an extensive study of potential vectors of these two exotic diseases in this country.

At the request of the Navy, a project for controlling the breeding of the mosquito that transmits dengue and yellow fever was instituted at Key West, Florida. Other projects of this type are being undertaken in Texas and South Carolina; they may also be needed at other points along the Atlantic seaboard. The problem of yellow fever has grown more acute as a result of plane travel between this country, West Africa and South America. A vaccine has been produced for this disease. The Public Health Service at the request of the War Department now supplies all the needs of the Army for yellow-fever vaccine to immunize troops.

The control of epidemic diseases, however, constitutes but a small part of the wartime activities of the Public Health Service. Another of our duties is the provision of medical care for merchant seamen and for the entire personnel of the Coast Guard, including the SPARS. Others treated at the marine and contract hospitals are veterans, civil-service personnel injured in line of duty and other legal beneficiaries. These hospital activities have of course been increased by the war. Our program for medical and hospital care of merchant seamen, for example, has been greatly expanded in a co-operative effort with the War Shipping Administration. Formerly a vast majority of seagoing merchant vessels had no first-aid or sanitation service of any kind. The United States Marine Hospital Corps School in Brooklyn, New York, graduated its first class of two hundred and thirty-nine pharmacist's mates on March 12 after six months of intensive training. This training program and other services — such as the psychiatric treatment of merchant seamen — are joint programs of the Public Health Service and the War Shipping Administration.

At the request of the Secretary of War a number of medical officers, engineers and sanitarians have been assigned to duty with the Army. We have men in each of the ten service commands, at the School for Military Government in Charlottesville and in Panama, Trinidad, Australia, Alaska and North Africa. Several who were on duty in the Philippines have been reported as prisoners of war. Industrial-hygiene experts are serving with the Ordnance Branch of the Army. A number of men have been assigned to duty in different parts of South and Central America in connection with the prevention of the spread of disease from one country to another, and in this country also a group of men are supervising sanitary conditions along the Pan American Highway.

Thousands of Public Health Service personnel are now working in several hundred war areas on assignment to the states, with others assigned to special regional and liaison programs. These are engaged in general public-health work, in industrial-hygiene services, in malaria, typhus, yellow fever and tuberculosis control and in the Civilian Defense plasma-bank programs.

In addition, we offer direct and co-operative services to such war agencies as the Federal Public Housing Authority, the War Production Board, the Federal Works Agency, the Office of Civilian Defense and the War Manpower Commission.

A very important part of our wartime work is assistance in the provision and training of professional personnel. As is generally known, there is an urgent shortage of physicians and dentists in certain critical war areas. Whenever it is impossible to meet the demands for medical care through the Procurement and Assignment Service, the Public Health Service is called on to meet them. Because of the shortage of nurses for the Army, the Navy and essential civilian tasks, we have attempted to increase the supply by stimulating enrollment in schools of nursing and by retraining inactive nurses.

A great portion of our work today is concerned with direct research on wartime problems. Studies now under way for the military authorities include an effort to find a preventive for malaria, the so-

lution of many intricate problems involved in combat flying, improvement in typhus-fever vaccine and other studies that, for military reasons, I cannot describe. Suffice it to say that the military authorities consider these studies of urgent importance.

Research concerning the toxicity and potential dangers of new substances prior to their introduction into industry is constantly going on. These studies are of the utmost industrial importance at this time.

Recently a member of the staff of the National Cancer Institute has succeeded in transforming normal cells grown artificially in the test tube into cancer cells by exposing the cultures to extremely small amounts of a coal-tar chemical that has long been known to induce cancer when injected into experimental animals. The transformed cells when reinjected into animals of the same species from which they were derived have grown rapidly, invading the other tissues of the body and finally killing the animals. It is probable that this contribution will lead ultimately to the discovery of the cause of cancer, since it demonstrates conclusively that the cancer process is started in single cells and is not dependent on constitutional conditions of the whole body. Owing to the increasing recognition of the high incidence of primary cancer of the lung, the National Cancer Institute has made a study of dust collected from a number of industrial cities. It was found, in two successive years, that these dusts contain tar that produces malignant tumors in mice. It is important that these studies be continued. Work is proceeding along the line of developing a chemical treatment for cancer, since the limitations of x-ray and surgery in the treatment for cancer are well recognized. Interesting leads have already been obtained from substances of bacterial origin. Work is now being done at the Cancer Institute on the development of methods for accelerating the healing of war wounds. Wound healing involves the study of cell growth and proliferation, a field with which research workers in cancer are thoroughly familiar.

A method for relieving the pain of childbirth was developed by two young officers of the Public Health Service at the Marine Hospital in Stapleton, New York, in the past year. Leaders in the medical profession consider this an outstanding contribution. It is an application of the principles of local anesthesia in that it is essentially a process whereby the larger nerves supplying the part of the body involved remain anesthetized throughout the period of painful labor. Mothers remain completely conscious throughout, and, having experienced this relief, are most enthusiastic about the method. The baby being born is not at all affected. Physicians who have witnessed demonstrations have been greatly impressed. The technic is somewhat difficult and requires special ability on the part of the physician. The method is known as continuous caudal analgesia. Possibilities for its use exist in fields of surgery other than obstetrics. The originators have demonstrated their technic at a number of medical schools and are receiving many requests for additional demonstrations.

With the tremendous growth in industry there has been a correspondingly increased need for looking after the health of the workers in the shipyards and munitions plants and for the expansion of health and sanitation activities in all war-industrial areas. For many years we have carried out studies on industrial hygiene. These have now been expanded, field staffs have been organized, and intensive programs to ensure the health of the industrial workers have been instituted. This is done by direct inspections of plants, especially government arsenals, and through forty-four industrial-hygiene units—in thirty-six states, four cities, two counties, the Tennessee Valley Authority and the District of Columbia. The work of state units is so integrated with that of the Public Health Service that a nationwide organization now exists that, if properly implemented, can serve effectively to guard the health of war workers. In connection with the protection of the health of industrial workers, a great deal of work has had to be done in war-industry areas, which grew up nearly overnight in connection with the lack of health and sanitation facilities.

Virtually all Public Health Service research, of course, has been turned to new problems rising from wartime needs. A number of our activities have been in force for a long time, however, although they have been given an additional impetus by the global war. Such are the programs for the control of venereal disease, tuberculosis and malaria.

Mobilization, vast industrial expansion and other conditions of war furnish ideal mediums for the spread of venereal disease. The Public Health Service has co-operated with the military authorities and state and local health organizations in improving conditions in many war-boom communities caught with no defense against venereal infections. The thirty-three hundred venereal disease clinics in the country last year represent a rise of 300 per cent over 1938. Over 10,500,000 treatments for syphilis were given by public-health officers last year, and 64 per cent of the men rejected for military service because of syphilis have already been brought under treatment. Twenty-two rapid-treatment centers for women who are spreading the

disease have been established, and we expect to have sixty more by the end of 1943. Our methods include the new intensive treatments for syphilis and the use of sulfonamide drugs for gonorrhea.

In anticipation of an expected war rise in the incidence of tuberculosis, the Public Health Service strengthened its prevention program by establishing an Office for Tuberculosis Control shortly after the war began. X-ray examinations have been given to nearly 250,000 people, over 160,000 of these being war workers in shipyards, ordnance plants, air depots and other essential war establishments. It is planned to extend the program to include the families of war workers and draft rejectees. All Coast Guard recruits are now examined by this method. We have also been examining Mexican laborers imported into the United States for work in agriculture, mining and railroading. The x-ray examinations are made by means of a cheap microfilm technic and the use of portable 35-mm. photofluorographic units.

The Public Health Service has had the primary responsibility for the control of malaria in all areas adjacent to naval and military establishments. This work has involved the organization of physicians, engineers, entomologists and other health personnel in a functional and co-operative unit for the basic purpose of eradicating the malaria mosquito. We have protected millions of war workers against the disease. As a result of these activities, too, the Army in 1942 reported the lowest annual malaria rate in its history, 0.6 per 1000 men.

* * *

All this gives a rough idea of what is being done by the United States Public Health Service to maintain the health of the Nation. Much has been and is being accomplished, but much, of course, still remains to be done.

THE EFFECT OF SULFANILAMIDE POWDER ON THE HEALING OF STERILE AND INFECTED WOUNDS*

With Special Reference to Tensile Strength and Ascorbic Acid Content in the Scar

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LOW tensile strength of healing wounds in scorbutic guinea pigs was reported by Lanman and Ingalls[1] in 1937 and by Taffel and Harvey[2] in 1938. In previous communications we[3] have demonstrated a direct relation between tensile strength and ascorbic acid content of healing wounds and the ascorbic acid intake in both guinea pigs and human beings.

Further studies of wound healing in guinea pigs maintained at varying levels of vitamin C intake are reported here. The chief object of these experiments has been to determine whether sulfanilamide powder placed in wounds produces any deleterious effect on the healing process. Such a study has seemed particularly timely at the present moment, when the use of this preparation in war wounds has attained such proportions. Although there can be no doubt of the efficacy of a procedure of this kind in controlling wound sepsis, it has seemed pertinent to ascertain whether the indiscriminate use of such a chemotherapeutic agent may interfere in any way with the formation of adequately healed wounds. In addition, we have studied the ascorbic acid content and tensile strength of healing wounds in the presence of induced wound infection or focal infection experimentally produced at a distance from an operative wound, with and without local sulfanilamide therapy and at various levels of ascorbic acid intake.

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PROCEDURE

The animals forming the basis of the experiments were divided into three main groups. Group A included guinea pigs of comparable size and age that were maintained on a scorbutic diet throughout the period of study; Group B included animals on the same scorbutic diet with a daily supplement of 1.5 mg. of ascorbic acid; Group C was made up of animals on the same basic diet with a daily supplement of 15 mg. of ascorbic acid. The basic scorbutic diet was that used in previous experiments and originally described by McCullough.[4] The ascorbic acid supplements were given in aqueous solutions and were administered orally twice a day by medicine dropper. The animals were maintained on these diets for a preliminary

period of two weeks, previously found to be adequate to establish a tissue level of ascorbic acid.

At the end of this period, an incision of the abdominal wall was made in all the animals, with the following complementary procedures on the basis of a preliminary subgrouping:

Subgroup 1 (control group): No other procedure.

Subgroup 2: Sulfanilamide powder inserted in operative wound.

Subgroup 3: Infection induced distant from operative wound.

Subgroup 4: Infection induced distant from operative wound; sulfanilamide powder inserted in operative wound.

Subgroup 5: Infection induced in operative wound.

Subgroup 6: Infection induced in operative wound and sulfanilamide powder inserted.

The operative procedure was as follows. Under ether anesthesia and surgical asepsis, a midline abdominal incision was made extending from the xiphoid to a point just below the umbilicus. A strip of tissue adjacent to the wound and consisting of the full thickness of the abdominal wall was excised for a control ascorbic acid assay. The peritoneum and muscular layers were closed in a single layer with a running suture of fine silk. The skin was closed in a similar manner in Subgroups 1 and 3. In Subgroups 2 and 4, 0.1 gm. of sulfanilamide powder was sprinkled over the muscle suture before closing the skin. In Subgroups 3 and 4, an infection distant from the operative wound was produced by subcutaneous inoculation with 1 cc. of a broth suspension of a blood-agar culture of beta-hemolytic streptococci. This inoculation was made from three to six hours postoperatively and a walled-off abscess invariably resulted at the site of the inoculation. In Subgroups 5 and 6, the muscle layer was smeared with a ground-up culture of beta-hemolytic streptococci before closing the skin incision, but in the latter group 0.1 gm. of sulfanilamide powder was sprinkled over the streptococcal smear before closing the skin incision.

In each main group the same dietary conditions that had prevailed preoperatively were continued throughout a ten-day period of healing, at the end of which time the animals were killed and the scars were assayed for ascorbic acid content of the tissue and for tensile strength (Table 1). The ascorbic acid content was determined by the method described by Bessey.[5] The tensile strength was measured by the application of a direct pull on the healing scar. The apparatus consisted of a 5-cc. glass syringe with collars mounted on the barrel and plunger. Each collar carried a bar pivoted at the center bearing two pins 1 cm. apart. The pivot provided an equalized pull on the tissue mounted on the pins when tension was applied by means of weights placed on the platform. The tissue was mounted on two rather than four pins to allow duplicate determinations on each wound through the use of narrow strips of tissue. As a result of these duplicate determinations, it became evident that there was considerable variation by this method and that only gross differences should be considered as significant. The tensile strength recorded is the weight necessary to rupture the muscle layer rather than the skin layer, as in every case the skin separated first. In scars of high tensile strength the adjacent tissue by which the specimen was mounted tore before the scar itself ruptured. For this reason, figures for tensile strength represent comparative, not absolute, values.

Results

The results obtained in these three groups of animals were as follows:

Group A. As might have been expected from previous studies, the operative wounds in all animals on a scorbutic diet with no ascorbic acid supplement showed little or no evidence of healing. In most cases, although there was some healing of the muscle layer, the skin edges at the site of the abdominal incision fell apart when the sutures were removed. The area of the scar was edematous and inflamed, and in a large percentage of the animals only a scab or a brittle layer of necrotic tissue was formed. Although the muscle layer showed evidence of healing, it required but slight traction to separate the wound. The average tissue ascorbic acid level in this group was very low, regardless of the experimental procedure employed. In the preoperative specimens it averaged 0.32 mg. per 100 gm. of tissue, and in the scars excised after ten days, 0.66 mg. Correspondingly low tensile strengths were noted, the average for the group being the equivalent of a pull of 157 gm. The preoperative values of tissue ascorbic acid in this group corresponded closely to the results reported previously by us[3] (0.23 mg. per 100 gm.). Regardless of the additional procedure utilized, no essential difference was noted in any of the animals regarding wound healing, ascorbic acid content of the operative scar or tensile strength. It will be noted that even in this vitamin C-deficient group there was no important deviation from the general average of scar-tissue ascorbic

acid content or of tensile strength in those cases where sulfanilamide powder was introduced into the wound. The lowest figures for tensile strength were those recorded in the animals in which the operative scar had purposely been infected (Subgroups 5 and 6).

Group B. A distinct contrast was observed in the animals maintained on a scorbutic diet plus a supplement of 1.5 mg. of ascorbic acid. As was to be expected, the average ascorbic acid content of the tissue was markedly higher than in the frankly scorbutic guinea pigs of Group A. The average tissue content of ascorbic acid in the preoperative specimens was 0.81 mg. per 100 gm., nearly three times that found in the scorbutic animals. In the ten-day scar the average figure of 2.34 mg. per 100 gm. was obtained, nearly a fourfold increase. The tensile strength of the scar was more than five times greater than that in Group A, the average being 853 gm. In these guinea pigs failure of the scar to heal completely was evident only in animals with induced infection in the operative wounds, and this was observed only in those not treated with sulfanilamide (Subgroup 5).

Group C. The guinea pigs in Group C, in which the diet was supplemented by the daily administration of 15 mg. of ascorbic acid, likewise showed excellent wound healing and, as was to be expected, high ascorbic acid assays of both the preoperative tissue and the scar, — 1.56 mg. and 5.14 mg., respectively. The average figure for tensile strength, 825 gm., was essentially the same as that noted in those receiving a smaller supplement of vitamin C. In one pig (Subgroup 5) with an infected operative wound, a section of the scar that was badly infected and oozing showed a tensile strength of only 125 gm., but the remainder of the wound, which was clean and well healed, resisted a pull of 825 gm.

Although there were occasional wide variations in tissue and scar vitamin C values and in estimations of tensile strength, these were exceptional and in no way altered the trend of the figures obtained in the three main groups. In general, the variations seemed to depend on the nutrition of the animals and on the presence or absence of intercurrent infection. The appearance of the healing wounds in the Group C animals was distinctly better than that noted in those which received a smaller supplementary feeding of vitamin C. In view of a striking increase in ascorbic acid concentration in the scar tissue, the failure to record an increased tensile strength was surprising. Such an apparent discrepancy may be accounted for by the fact that it was rarely possible to measure higher tensile strengths than the average recorded figures because by the method employed the adjacent tissue failed to withstand the additional traction caused by increased weight.

A point of some interest was noted in the scorbutic animals (Group A). In Subgroup 3 distant

TABLE 1. *Ascorbic Acid Content and Tensile Strength of Scars in Guinea Pigs under Varying Conditions of Vitamin C Intake and Varying Experimental Procedures.*

GROUP	SUBGROUP	NO. OF ANIMALS	AVERAGE ASCORBIC ACID CONTENT		AVERAGE TENSILE STRENGTH OF SCAR
			PREOPERATIVE TISSUE	SCAR TISSUE	
			mg./100 gm.	mg./100 gm.	gm.
A: Animals on basic scorbutic diet	1: Operation only	7	0.13	1.49	190
	2: Sulfanilamide in wound	4	0.00	0.12	260
	3: Distant infection	4	1.05	0.56	180
	4: Distant infection; sulfanilamide in wound	6	0.01	0.51	170
	5: Infection in wound	5	0.39	0.61	80
	6: Infection and sulfanilamide in wound	4	0.35	0.71	60
	Averages		0.32	0.66	157
B: Animals on basic scorbutic diet with daily supplement of 1.5 mg. of ascorbic acid	1: Operation only	4	1.19	2.31	670
	2: Sulfanilamide in wound	2	0.80	2.24	900
	3: Distant infection	5	1.07	2.82	800
	4: Distant infection; sulfanilamide in wound	3	0.79	2.87	850
	5: Infection in wound	4	0.26	2.15	740
	6: Infection and sulfanilamide in wound	4	0.77	1.68	1160
	Averages		0.81	2.34	853
C: Animals on basic scorbutic diet with daily supplement of 15 mg. of ascorbic acid	1: Operation only	4	1.92	3.78	740
	2: Sulfanilamide in wound	4	2.64	6.25	540
	3: Distant infection	3	1.62	5.02	690
	4: Distant infection; sulfanilamide in wound	4	1.14	4.75	640
	5: Infection in wound	5	1.04	5.84	780
	6: Infection and sulfanilamide in wound	5	1.00	5.21	1560
	Averages		1.56	5.14	825

infection was produced by experimental abscess formation at a site far from the operative scar. At the end of the ten-day postoperative period it was possible to isolate in the operative scar, which was poorly healed, the same strain of organisms that had originally been used in producing the abscess.

An additional point of interest lies in the apparent effect of vitamin C and sulfanilamide therapy in reducing the mortality in all groups incident to the experimental procedures involving wound infection (Subgroups 5 and 6). During the course of these experiments 30 animals died before the expiration of the ten-day postoperative period. Tissue studies on these animals were not included in the results tabulated in Table 1. Death apparently resulted from infection or infection together with vitamin C lack. In Table 2 are given the mortality figures as they occurred in the three main groups. Of the scorbutic animals (Group A) with streptococcal infection of the operative wound and no supplement of ascorbic acid, 72 per cent succumbed. Where sulfanilamide powder was placed in the wound, 43 per cent of a smaller group died. Of the animals receiving a daily supplement of 1.5 mg. of ascorbic acid (Group B), 71 per cent failed to survive when sulfanilamide powder was not used. When the drug was employed, however, only 20 per cent died. Among the animals receiving a maximum daily supplement of 15 mg. of ascorbic acid (Group C), only 17 per cent died. The use of sulfanilamide had no apparent effect on this mortality.

TABLE 2. *Mortality Rate in Animals with Infected Wounds.*

CLASSIFICATION	GROUP A			GROUP B			GROUP C		
	NO. OF ANIMALS	NO. OF DEATHS	MORTALITY %	NO. OF ANIMALS	NO. OF DEATHS	MORTALITY %	NO. OF ANIMALS	NO. OF DEATHS	MORTALITY %
Subgroup 5:									
Wound infection without sulfanilamide	18	13	72	14	10	71	6	1	17
Subgroup 6:									
Wound infection with sulfanilamide	7	3	43	5	1	20	6	1	17

DISCUSSION

Although occasional single determinations of tissue ascorbic acid and tensile strength varied considerably, no important discrepancies were noted. In entire accord with previous results,[3] it has been shown that vitamin C lack in guinea pigs is associated with low tissue values for ascorbic acid, poor wound healing, low ascorbic acid values and correspondingly low tensile strength in healing scars. Minor variations in ascorbic acid values appeared to depend on the general condition of single animals. Occasional discrepancies in the estimations of tensile strength were undoubtedly due to inadequacies in the technical method employed. Nevertheless, the trends in the three main groups were consistent. Failure to obtain maximum increases in the tensile strength of scars commensurate with the increase in ascorbic acid content following high supplements of vitamin C was probably associated with a technical failure to register values above certain levels because of the relative weakness of adjacent tissues. It is highly probable that the greater supplements of vitamin C were associated with the formation of extremely strong scars.

From the results obtained, it is clear that the use of sulfanilamide powder under varying experimental conditions in no way retarded healing or resulted in inefficient scar formation. Furthermore, the analysis of vitamin C content of preoperative tissue specimens and ten-day scars reveals no evidence that sulfanilamide caused a deviation of ascorbic acid away from scar tissue or increased the need of ascorbic acid in the production of a normal strong cicatrix. In the presence of serious ascorbic acid lack the use of the drug was not effective in promoting better wound healing and a single local dose did not adequately control wound infection. In all three groups of animals there seemed to be one constant factor contributing to poor wound healing. This factor was local infection in the wound. In those animals receiving adequate or massive supplements of ascorbic acid, wound infection was more nearly controlled by sulfanilamide therapy. In the few cases where the infection was not completely controlled, a strong scar was not obtained. An excellent illustration of this fact has already been mentioned in the preceding section. In this case the tensile strength of the uninfected portion of the scar was nearly seven times that of the adjacent portion of the scar, which still showed evidence of sepsis. Obviously, impaired healing was due not to the deleterious action of the drug but to its failure to control completely the local in-

fection. In this connection it is pertinent to point out that the lowest tensile strength recorded in the operative scars was observed in the animals with scurvy and wound infection (Group A, Subgroups 5 and 6). It is highly probable that fewer failures to obtain good scars in infected wounds in the animals on vitamin C supplements would have occurred with the supplementary use of oral chemotherapy.

The mortality figures given in Table 2 suggest that optimal concentrations of ascorbic acid in tissues increase their resistance to infection. The actual number of animals employed was obviously too small to warrant anything but the suggestion. One cannot overlook, however, the striking difference in mortality in the animals with induced wound infection in Groups B and C in which no local chemotherapeutic agent had been employed. Such a difference in mortality conceivably represents a difference in tissue resistance to infection resulting from optimal rather than moderate tissue saturation with ascorbic acid. The actual difference in the tissue ascorbic acid values in the two groups may represent confirmatory evidence of such a point of view. Further confirmation is implied by the fact that in the scorbutic animals (Group A) the production of focal walled-off abscesses distant from the operative scar was followed by ultimate infection of the scar with the same organism. Further, carefully controlled studies are needed on such a debatable point, but it seems important to call attention to the possibility that maximal tissue saturation with ascorbic acid may increase tissue resistance to infection as well as promote optimal conditions for wound healing.

Conclusions

As shown in previous studies, the ascorbic acid content of healing wounds in guinea pigs varied with the ascorbic acid intake. Such variations were in no way influenced by the presence of local or distant infection or by the introduction of sulfanilamide into the operative wound.

The tensile strength of healing wounds varied with the intake of ascorbic acid and the resulting ascorbic acid content of the scar.

The use of sulfanilamide in the healing wound did not reduce the tensile strength of the scar.

The presence of focal infection distant from the healing scar did not alter its ascorbic acid content or tensile strength. Local wound sepsis, however, in numerous cases reduced tensile strength and interfered with normal healing. This was particularly marked in scorbutic animals but also occurred when local sulfanilamide therapy was not completely effective.

Certain of the results obtained in these studies suggest that maximal saturation of tissues with ascorbic acid aids in providing optimal tissue resistance to infection.

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RHINOSCLEROMA*

Report of a Case

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SCHENECTADY, NEW YORK

RHINOSCLEROMA is a chronic granuloma of the upper respiratory tract and was first described by Hebra[1] in 1870. The disease is common among the lower classes in the rural sections of central Europe and is often encountered in Italy and Egypt. It is also seen in other lands[2, 3] and has been reported in this country, where cases were observed in the northern states. It is distinctly associated with a poor hygienic environment, and there is evidence that it is mildly contagious.

The disease is rarely seen in the United States, and usually occurs in foreign-born persons.[4] There is a recorded case in a native-born American living in New Jersey, who, however, had Slav parents.[5] Doubtless, additional cases would be discovered were familiarity with the disease more general. Weiss[6] in 1939 recorded 8 cases in native Americans. Later Simpson and Ellis[7] reported a case in a native of North Carolina, Abascal[8] and Pardo-Castello and Dominquez,[9] cases studied in Cuba. In regions where rhinoscleroma is considered rare, it is being recognized with increasing frequency, probably owing to improved diagnosis, especially by biopsy. After the present war with the tremendous shifting of peoples in Europe and elsewhere, the disease may be found oftener, and undoubtedly in areas hitherto free from it.

In most patients, rhinoscleroma appears to begin in the anterior nares and slowly spreads to the lip, nose, pharynx, palate, larynx and trachea. Pri-

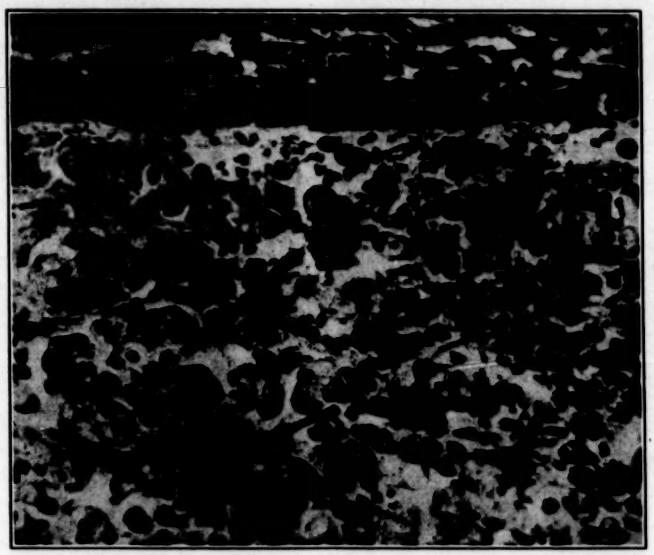

FIGURE 1. *A Lesion from the Roof of the Mouth Showing the Type of Cellular Reaction (× 500).*

The endothelial leukocytes are filled with micro-organisms; there are numerous plasma cells and polymorphonuclear leukocytes.

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marily an infiltrative, inflammatory process, it may be combined with or replaced by sclerosis, atrophy and scarring of the mucosa. The chief

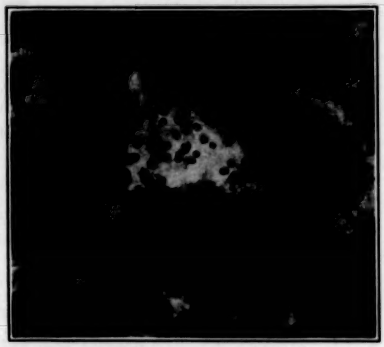

FIGURE 2. Klebsiella rhinoscleromatis *in a Space in the Squamous Epithelial Layer* (× 1400). *The capsules are stained.*

gross features are hard, infiltrated tissues, hard, granular, atrophic mucous membranes that bleed readily on manipulation and a marked fetid odor. Frequently cancer or tuberculosis is the initial clinical diagnosis, because of the prolonged course of the disease.

The disease must be differentiated from several other conditions with which it may be confused. In the early stages, syphilis and lupus may be considered, and the later, more extensive process may suggest cancer or leprosy. The slowly progressive nature of the lesion, usually beginning before the age of forty, a history of origin in the nares or palate and a gradual spread to the entire nasopharynx emphasize the unusual nature of the process. Negative blood Wassermann reactions and failure to respond to antisyphilitic therapy exclude syphilis. Involvement of the lip may suggest keratosis follicularis (White's disease), which, however, is associated with general skin changes. Periarteritis nodosa, in which there are granulomatous lesions in the gastrointestinal tract, may be excluded by the absence of pain locally and in the abdomen. Since those affected frequently care for horses, chronic glanders must be excluded, and this may be done by bacteriologic studies and the Strauss reaction. Ultimately, a biopsy should be performed, which will lead to the correct diagnosis.

Microscopically, the lesion shows characteristic changes the dominant features of which are the inflammatory process and the presence of numerous, large, swollen, vacuolated endothelial cells containing encapsulated bacilli. These cells were first described by Mikulicz[10] in 1876, and the organism believed to be the cause of the infection was isolated by Frisch[11] in 1882. This bacterium is al-

FIGURE 3. *Minute Abscess in the Squamous-Cell Layer* (× 750). *It is filled with bacilli and polymorphonuclear leukocytes; none of the organisms are phagocytized.*

most identical with Friedländer's bacillus (*Klebsiella pneumoniae*).

Case Report

A 66-year-old man, born in Poland, had been a resident of Berkshire County, Massachusetts, for many years. During most of that time he had worked intermittently as a laborer and lived in the country under simple hygienic conditions. He was seen for the first time by a physician in September, 1928, when he visited Dr. F. S. Gospodarek of Adams, Massachusetts, complaining of a mouth condition that he stated had been present at least five years

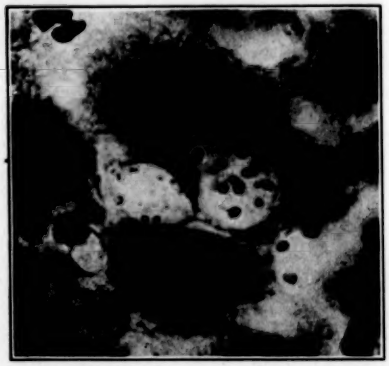

Figure 4. *Endothelial Leukocytes in the Epidermis (× 1600).*

One contains bacilli with well-developed capsules; the other, bacilli without capsules.

and that had begun to interfere with eating and swallowing. He was certain that the trouble began after a tooth extraction. The mouth was tender but not painful. He had not lost weight and recalled no gastrointestinal symptoms. No other member of the family, which included four children, showed evidence of similar changes in the mouth or nose.

Examination showed a dusky-red, thickened, granular, indurated lesion involving the hard and soft palate. In addition to small and large granulations on the surface there were many deep grooves mingled with grayish areas, apparently cicatrices. The uvula was absent. The process involved the postpharyngeal wall as far as one could see, and also the gum margin of the upper jaw on the left side. On palpation the palate and contiguous buccal mucosa were exceedingly hard, suggesting a scirrhous carcinoma. Manipulation resulted in free bleeding from the surfaces. The nose and upper lip were apparently not involved, but a discharge was present in the nostrils, as well as a foul, fetid odor.

Sections of a small fragment of tissue from the hard palate showed an inflammatory lesion characterized by the presence in the epithelium and subepithelial tissue of large, pale, rounded cells of endothelial type, each containing clear, foamy cytoplasm and as many as forty somewhat regularly distributed minute rods lying in clear spaces (Figs. 1–5). In some cells the organisms possessed well-defined capsules; in fields where the capsules were absent there were numerous polymorphonuclear leukocytes. The nuclei were small, round and pyknotic and placed in the centers or peripheries of the cells.

Cultures of the nose and palate on a variety of mediums yielded mixed growths in which large, clear, colorless mucoid colonies were a prominent feature. They developed best on human blood agar and attained a diameter of 10 mm. The organisms were short, plump, nonmotile, gram-negative rods with rounded ends, and varied in size from 2 to 8 microns, depending on the growth period. The bacterium was very aerobic, growing best on or near the surface and forming in broth a thick pellicle. Gelatin and Loeffler's serum were not liquefied. Litmus milk was faintly and slowly acidified, and in the various carbohydrate mediums, except lactose, there was acid production but no gas. The organism did not develop on highly acid mediums. Indole was not produced. Cultures were odorless, and the organism resisted drying for 2 weeks.

The patient was next seen in October, 1939. He was then a short and emaciated man and weighed only 90 pounds. Because of increasing difficulty in breathing, a tracheotomy had been performed several months previously. The breath from the tracheal tube was extremely

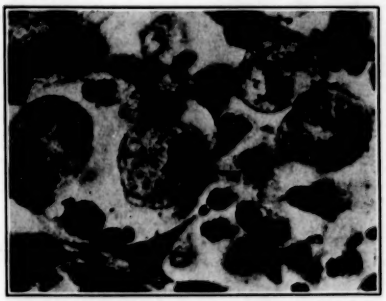

Figure 5. *Endothelial Leukocytes Filled with Bacilli of Rhinoscleroma (× 1100).*

fetid. The voice was fairly audible. There were no external signs of the disease about the nose or lips.

Examination of the mouth disclosed a greatly contracted oral cavity. The deformed, thickened, granular, scarred palate was drawn down toward the base of the tongue, reducing the oral cavity to about a fourth of its normal volume. The process involved the buccal mucosa, particularly on the left side, to which the base of the tongue was adherent. The tonsils were not visible. The tongue was soft and coated. The anterior gum margins were not involved by the process. Slight rubbing of the palate surfaces resulted in free bleeding. The nasal mucosa was markedly congested but did not resemble the oral membrane. During the preceding 12 years the patient had received only local treatment. As he was living on a remote farm and was somewhat indifferent to medical advice, therapeutic procedures were not adhered to.

A second biopsy was performed in October, 1939, and

sections showed the same type of pathologic change described above. The endothelial cells containing Frisch bacilli were much more abundant than previously. Numerous colonies of the same organism were obtained on plain agar slants from the mouth but fewer colonies from the nose. Cultures made from the fingers by impressing them on agar plates also yielded a few of the same type of colony, and swabbings from the rectum yielded an abundant growth of colonies identical with those obtained from the mouth. Thus, an organism of the Friedländer type was isolated from the nose, mouth, fingers and rectum that was identical with the bacillus isolated 11 years previously.

The patient died in March, 1942, about 20 years after the onset of the disease. The lesion had become slightly more extensive, the fetid odor was more pronounced, and the patient could not breathe without a tracheotomy tube but swallowed liquids well. The terminal symptoms indicated failing heart action. Permission for autopsy was not obtained.

The organism was apparently a member of the coliaerogenes group. It was cultivated in broth and as much as 2 cc. of 18-hour broth cultures was injected subcutaneously and intraperitoneally into guinea pigs and intraperitoneally and intravenously into rabbits, but symptoms were not induced. Subcultured over a period of 14 years the organism still retains its original characteristics and resembles members of the genus Klebsiella.

The bacterium corresponds closely with *K. rhinoscleromatis*, described in 1882 by Frisch.[11] He believed it to be the cause of scleroma and by injections into the nasal septum of rats was able to produce small tumors. Many other workers have been unable to develop lesions in ordinary laboratory animals with injections of this organism, and its etiologic role is still uncertain.

* * *

In this case report the points deserving special attention are the specific pathologic changes of the disease, the presence of capsulated gram-negative bacilli in the large endothelial cells and the constant presence in ordinary cultures of *Klebsiella rhinoscleromatis*.

I am indebted to the late Dr. Frank B. Mallory for assistance in the diagnosis and for the photomicrographs.

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CLINICAL NOTE

PROLONGED URETERAL OBSTRUCTION WITH RECOVERY FOLLOWING ADMINISTRATION OF SULFADIAZINE AND SULFATHIAZOLE*

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RENAL complications following the use of sulfapyridine,[1, 2] sulfathiazole[3, 4] and sulfadiazine[5–7] may be of serious consequence, with death in some cases rapidly following the development of anuria and uremia. On the other hand, sulfanilamide is much less likely to injure the kidney seriously.[4] According to Keefer,[8] "it is rare indeed for a patient who has shown signs of renal insufficiency during sulfonamide therapy to continue to show them following the termination of treatment." Most authors agree on the treatment of acute manifestations of renal complications; namely, discontinuance of the drug, forcing of fluids and ureteral catheterization and irrigation when oliguria persists or anuria develops.

FIGURE 1. *Dilatation of the Left Upper Ureter, Kidney Pelvis and Calyxes Due to Obstruction of Ureter by Sulfonamide Crystals.*

Prolonged toxic reactions following the administration of sulfanilamide and its derivatives are unusual. Review of the literature fails to reveal reports of persistent urinary findings after the sulfonamide has been stopped. The normal pattern of toxicity is manifested by its appearance during administration and its prompt relief on discontinuance. The case reported below is uncommon in that ureteral obstruction persisted for more than two months after discontinuance of the sulfonamide and was completely relieved by ureteral catheterization and irrigation.

CASE REPORT

A. L., a 27-year-old soldier, was admitted to the Medical Service of the Lovell General Hospital on June 11, 1942, complaining of generalized malaise and fever with some aching of the legs and arms of 1 week's duration. On June 9, there had been an attack of vomiting, which was attributed to overeating. The day before admission he felt feverish and the temperature was 101°F. Physical examination was entirely normal, and the patient denied having venereal disease. He had previously been observed at this station in May, for German measles and after 1 week's stay was discharged apparently fully recovered.

FIGURE 2. *Normal Ureter and Kidney Pelvis after Obstruction of the Left Ureter Was Relieved by Catheterization and Irrigation.*

Examination showed a well-developed and well-nourished man who appeared ill but not seriously so. The temperature was 99.8°F., the pulse 88, and the blood

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pressure 130/90. The only abnormal physical finding was mild circumorbital edema.

The initial urinalysis revealed a moderate amount of albumin. Microscopic examination of the sediment showed abundant white cells with frequent clumping, an occasional pus cast and 5 to 7 red cells per high-power field. A Kahn test was negative. The sedimentation rate was markedly increased. The white-cell count was 13,000, with 63 per cent polymorphonuclear neutrophils, 7 per cent stab forms, 4 per cent eosinophils, 23 per cent lymphocytes and 3 per cent monocytes. The red-cell count was 4,400,000, with 100 per cent hemoglobin. The blood nonprotein nitrogen was 43.5 mg. per 100 cc. Daily urinalyses revealed persistent albuminuria, pyuria and hematuria.

With these findings in mind, the patient was questioned further and gave the following history. On May 15, after sexual relations 3 days previously, he noted a thin, watery urethral discharge associated with burning, itching and frequency of urination. He consulted a civilian physician, who prescribed sulfadiazine, of which he took 44 gm. over a period of 10 days. At the completion of this course of therapy, the discharge persisted and there was pain in the left upper quadrant of the abdomen associated with the passage of yellowish brown urine. After all medication had been discontinued for 10 days, sulfathiazole was prescribed and 12 gm. was given in 2 days. Ten days later malaise and fever were noted and were the chief complaints on admission.

It seemed likely that the patient was suffering from sulfonamide lithiasis. Accordingly, fluids were forced, the urine being observed closely in an effort to clear the genitourinary tract. In spite of adequate fluid intake and output, the abnormal urinary findings continued. A scout film of the abdomen showed no signs of calculus. On July 13, intravenous and retrograde pyelograms revealed poor function of the left kidney with considerable dilatation and blunting of pelvis and calyxes. The lower four fifths of the left ureter was not visualized. There were no visible urinary calculi (Fig. 1). On July 17, the left ureter was catheterized and 10 cc. of foul-smelling, turbid urine was recovered. Microscopic examination revealed many red cells but no organisms. Guinea-pig inoculation was negative for tuberculosis. On July 25, examination of a centrifuged specimen of urine revealed numerous white cells, many sulfadiazine crystals and a chemical determination of 218 mg. of sulfadiazine per 100 cc. The patient became afebrile soon after admission. On August 18, the ureters were again catheterized. The left kidney pelvis was irrigated with diluted acetic acid and a dark, grumous urine with heavy sediment was recovered. Following this a steady drip of clear urine was observed coming from the left ureter. Urograms revealed complete disappearance of the previously described dilatation of the left upper urinary tract, with normally appearing kidneys and ureters (Fig. 2). Following this the patient had an uneventful recovery, the urine cleared, the sedimentation rate fell, and blood urea nitrogen and renal-function tests returned to normal. The patient was returned to full duty on October 29.

Summary

A case of hydronephrosis and hydroureter with recovery that occurred after prolonged obstruction by sulfonamide crystals is reported.

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MEDICAL PROGRESS

PANCREATIC INSUFFICIENCY AND THE CELIAC SYNDROME

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THE chronic failure of nutrition in infants and children described by Gee[1] in 1888 under the term "the coeliac affection" is recognized today as a syndrome rather than a disease entity always caused by the same etiologic factor. Only in recent years has an approach been made to an understanding of some of the conditions that produce the celiac picture. Gee himself remarked that "naked-eye examination of dead bodies throws no light upon the nature of the coeliac affection," and Parsons[2] in the Rachford Lectures described the results of pathological studies in true celiac disease as follows: "The finding, after much scratching about, of some small grains of reward in the shape of an alteration in a few cells does not seem sufficient to justify an exulting cackle, but rather should stimulate research in other directions."

Morbid anatomy has indeed thrown no light on the nature of the usually benign idiopathic celiac disease, but pathological studies have been responsible for a revival of intense clinical interest in the entire group of disorders bearing the celiac imprint. They have resulted, furthermore, in the discovery and characterization of clinical entities associated with pancreatic insufficiency in early life, including a condition until recently confused with idiopathic celiac disease. This condition, in contrast to what Parsons found in celiac disease, is characterized by important and easily demonstrable pathologic changes and is associated with pancreatic achylia produced by obstruction to the outflow of pancreatic juice. The present review will be limited to a consideration of this disorder, which has been variously termed "pancreatic insufficiency," "pancreatic steatorrhea," "pancreatic fibrosis," and "cystic fibrosis of the pancreas." The term "pancreatic achylia" will be used to describe the physiologic consequences of this obstructive lesion in the pancreas. Reference to true or idiopathic celiac disease will be made only when necessary for clarification of the subject matter. Results of studies at the Children's and Infants' hospitals, including unpublished data, will be drawn on throughout this account. The contributions of Parsons[2] and of Neale,[3] the monographs of Lehndorff and Mautner[4] and of Fanconi[5] and the recent summary of therapeutic and physiologic studies by May, McCreary and Blackfan[6] should be consulted by the reader interested in idiopathic celiac disease and the celiac syndrome.

The features that characterize the celiac syndrome include the typical wasting, more in the limbs than in the face; distention of the abdomen, which may be soft, doughy and inelastic or markedly distended and tight; bulky, foul-smelling, frothy stools that contain excess fat; and often retardation of growth. To these may be added clumping of barium in the small intestine, a flat glucose-tolerance curve and a low rise in the level of vitamin A in the blood during the vitamin A-absorption test.[6] These symptoms may appear as a result of congenital malformations of the small intestine or its attachment, chronic infections, dysentery, megacolon or pancreatic insufficiency. True or idiopathic celiac disease is used to describe this group of symptoms and laboratory findings in patients in whom no underlying disease can be found and who are improved and usually cured by treatment consisting of good general care and any one of the well-established celiac diets. Some idea of the difficulty of understanding the celiac syndrome may be obtained by reference to the large number of names applied to members of this group of diseases. These include acholia, intestinal infantilism, chronic intestinal indigestion, Heubner-Herter disease, Gee-Herter disease, pancreatic infantilism, chronic idiopathic steatorrhea, familial pancreatic insufficiency, indigenous sprue and pancreatic steatorrhea.

Since the time of Gee, true celiac disease has been differentiated with difficulty from a chronic failure of nutrition caused by pancreatic disease, with symptoms resembling those in true celiac disease so closely that the two conditions were considered by most observers to be identical. The striking nature of the clinical features of the celiac syndrome explains the neglect of the respiratory and other non-nutritional aspects of the disease associated with pancreatic insufficiency. The paucity of complete post-mortem studies and competent

The articles in the medical-progress series of 1941 have been published in book form (*Medical Progress Annual*. Volume III. 678 pp. Springfield, Illinois: Charles C Thomas, 1942. $5.00).

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clinicopathological correlations is responsible for the late recognition of the fact that the celiac picture is only one of a group of what had been thought to be several unrelated diseases caused by or associated with an obstructive lesion in the pancreas that produces pancreatic achylia.

Beginning about thirty years ago, scattered postmortem observations concerning the pancreas appeared in the literature on celiac disease. A marked increase in interlobular fibrous tissue of the pancreas, for example, was observed in 1914 by Poynton, Armstrong and Nabarro.[7] Passini[8] described actual pancreatic disease in an infant with nutritional failure. Some writers who found pancreatic lesions in patients with the celiac syndrome explained them as secondary to the failure of digestive secretion and function.[9] The relation of pancreatic insufficiency to the celiac syndrome was brought into clear perspective in 1935 by a short clinicopathological communication by Parmelee,[10] who referred to evidence gathered from the literature and reported 2 new cases of pancreatic disease. He suggested that what he called "congenital steatorrhea" differed from the usual picture of celiac disease in the early onset, the excessive amount of neutral fat in the stools and the uniformly fatal outcome. In these patients, at post-mortem examination there were found constant changes, including marked fibrosis and great diminution of secretory gland tissue in the pancreas, and bronchopneumonia, usually of a subacute type with purulent bronchitis and bronchiectasis. In 1935, Thaysen[11] grouped celiac disease, nontropical sprue and tropical sprue under the general heading of idiopathic steatorrhea. In the following year, Hanes and McBryde[12] stressed the identity of sprue and true celiac disease, and listed an impressive series of observations in favor of this conclusion. The logical analysis of Rauch, Litvak and Steiner[13] paid particular attention to steatorrhea, which was classified as the idiopathic variety, which includes true celiac disease, and the pancreatogenous variety.

Several independent investigations published in 1938 and 1939 crystallized the problem and marked the beginning of the recent series of contributions to the present knowledge of the clinical characteristics of this pancreatic disease, the methods of diagnosis and treatment and the nature of the underlying disorder. Comprehensive reviews of the literature may be found in the papers of Andersen[14] and of Rauch, Litvak and Steiner.[15] In 1938, Andersen gave a detailed analysis of the clinical and pathological findings in 49 cases of pancreatic fibrosis, which included 20 from the post-mortem files of the Babies' Hospital, New York City. Her studies gave strong support to the validity of the separation of pancreatic fibrosis from true celiac disease and emphasized the logical use of pancreatic-enzyme analysis as a valuable diagnostic measure and of pancreatic substitution therapy. In the same year, Blackfan and May[16] analyzed the clinical records of 35 cases selected from 2800 autopsies in the Department of Pathology of the Children's Hospital. These cases had been set apart as a pathologic entity because of the constant occurrence of an obstructive lesion of the pancreas, which was associated, however, with several different clinical pictures.

From the clinical analyses of Andersen and of Blackfan and May from a subsequent experience at the Children's Hospital,[16] it appears that the infants in whom obstructive lesions of the pancreas are found at autopsy may be divided into three clinical groups: those who died either in the first week or first few weeks of life, usually from meconium ileus; those who died, usually in the first year of life, with a clinical history of nutritional disturbance often obscured by respiratory disease, usually called chronic pneumonia or bronchitis, or bronchiectasis; and those with symptoms recognizable as preceliac and celiac who died of respiratory disease.

Group 1. The term "meconium ileus" is used to describe intestinal obstruction in the newborn caused by the inability of the intestine to propel through its lumen a thick, mucilaginous meconium, the altered physical state of which is explained by the failure of pancreatic enzymes, particularly trypsin, to act on it during intrauterine life.[17] Death has occurred almost invariably in infants with this severe type of intestinal obstruction. Lesser degrees of obstruction may be produced by inspissated meconium unassociated with pancreatic achylia, as in stenosis of the ileocecal valve. Post-mortem examination of patients with true meconium ileus reveals pancreatic fibrosis with obstruction to the outflow of secretions proved in some cases to be caused by congenital atresia or stenosis of the main pancreatic ducts. Absence of tryptic activity in the pancreatic juice has been demonstrated in one patient with meconium ileus, and in the duodenal content obtained at autopsy shortly after death in another. Dilute solutions of pancreatin added to the grossly altered mucilaginous meconium bring this material to a watery consistence. Successful attempts have been made to relieve the intestinal obstruction in meconium ileus by introducing a 1 per cent solution of pancreatin directly into the duodenum so that it may act on the altered meconium.[17] Recent reports of meconium ileus have been made by Hurwitt

and Arnheim[18] and by Kaufmann and Chamberlin,[19] who review the literature.

Group 2. Andersen[14] found that patients in this group usually died before six months of age, and that many of them presented feeding problems characterized by hunger, failure to gain weight and foul, bulky stools. A somewhat different summary was given by Blackfan and May,[15] who recognized that the clinical manifestations in this group were limited in variety but were common to so many disorders in infancy that a sharply defined clinical picture could not be drawn. Usually, these infants developed symptoms referable either to the gastrointestinal tract or to the respiratory system. Vomiting and diarrhea with failure to gain weight or loss of weight preceded the onset of signs of infection of the respiratory system in some cases, but in others a severe and nonproductive cough was an early complaint, followed later by a productive cough and physical signs of partial or complete obstruction of different parts of the bronchial tree. Vomiting was usually not present. Diarrhea was occasionally severe and often lasted for prolonged periods. The stools contained no pus or blood and were definitely not fatty. The average duration of the illness of the patients who lived beyond the neonatal period was six months. The average age at death in this group was eight months. The pertussis-like cough impressed Rauch and his co-workers[13] as a characteristic feature of this disease.

Group 3. About half the patients in Andersen's[14] series fell into this group, and ranged in age from six months to fourteen and a half years. They all died of pulmonary infection. Only one fifth of the patients described by Blackfan and May[15] were included with these cases, which possessed clinical features similar to those of true celiac disease, such as emaciation, distention of the abdomen and large, pale, putrefactive, fatty stools. All these patients died of pulmonary disease.

In our experience,[16] Group 2 is by far the largest and the cases in it are the most difficult to recognize, and Group 3 in which the condition closely resembles that of true celiac disease, is the smallest. It appears that the patients in all groups are apt to die before there is developed a clinical picture that can be confused with true celiac disease. It is probable that, as further experience with the disease is gathered, the cases in Group 2, in which the respiratory symptoms dominate the picture, will be divided into more distinctive clinical branches.

The familial aspect of this disease has been recognized. A number of cases have been recorded of two or three siblings with the same disease, as proved either by post-mortem examination or by pancreatic-enzyme analysis. The early onset of symptoms has caused the disease to be regarded as congenital.

It is probable that this pancreatic disease is much commoner than may be concluded from the number of cases reported in the literature. Andersen[14] found an incidence of 3 per cent in her post-mortem records. Blackfan and May[15] reported an incidence of 1.3 per cent among infants and children examined at autopsy up to 1937 at the Children's Hospital. In the same laboratory during the following six years ending with 1942, 52 cases of marked pancreatic fibrosis (4.8 per cent) were found among 1089 autopsies on infants and children, with meconium ileus in 13; in 1942, autopsies were performed on 198 cases, of which 16 (12 per cent) showed pancreatic fibrosis.[20] Early cases of the lesion consisting in inspissation of secretions only in the acini are now being frequently found in routine post-mortem studies on infants and children.[16]

Pathological Findings

The lesion in the pancreas seen most frequently in these patients is characterized by dilatation of ducts, inspissation of secretion, atrophy of acinar structures and replacement of connective tissue, leading to marked fibrosis of the organ.[14, 16] Congenital stenosis or atresia of the pancreatic ducts may be found. In most cases, obstruction appears to begin in the acini. The islets of Langerhans are not involved. The lesion may be recognizable grossly or may be complete histologically and functionally without visible gross change. No matter what the cause of the lesion, the effect of obstruction within the acini themselves is equivalent to that produced by ligation of the main pancreatic ducts. From this histologic picture, interference with the production, liberation or passage of pancreatic enzymes leading to pancreatic achylia may be expected.

Hyperexpansion and atelectasis, usually in combination, are the commonest early findings in the lungs, and these are explained by obstruction caused by the tenacious mucopurulent material usually found in the upper respiratory tract. In the more advanced cases of the disease, widespread bronchiectatic and bronchiolectatic abscesses are found. *Staphylococcus aureus* is usually the offending organism. Thickening of the bronchiolar walls, replacement fibrosis in those areas of the lungs repaired after staphylococcal destruction and diffuse bilateral acute and chronic bronchopneumonia characterize the later stages of the disease. Fundamentally the process in the lung is one of upper respiratory obstruction caused by thickened,

tenacious mucus, with secondary infection by *Staph. aureus*.[16]

Three explanations for the pulmonary lesions have been offered. Decreased resistance in a chronically ill patient with nutritional failure is an obvious conclusion. Secondly, metaplasia of bronchial epithelium caused by vitamin A deficiency has been held responsible for the secondary infection that follows mechanical obstruction and loss of ciliated epithelium.[14] This plays a role, but only in patients with evidence of vitamin A deficiency of important degree. The third explanation depends on the thick mucus produced in the tracheal and bronchial glands, which fails to lubricate properly the ciliated epithelium of the upper respiratory tract and so permits infection by a staphylococcus of low virulence.[16] More important than the infection is the obstruction caused by the tenacious mucus, comparable in consistence to the viscid pancreatic juice found in the duodenal content. This obstruction is the cause of most of the early signs of respiratory disease and is responsible for the bronchiectasis and later the bronchiectatic abscesses.

The liver is usually increased in size and shows fat metamorphosis. In rare cases there is an unusual form of biliary cirrhosis characterized by a lesion resembling closely that in the pancreas.[20] Inspissation of secretions in the ducts and acini of the salivary glands and in the mucous glands of the trachea, bronchi, esophagus and gall bladder occurs with such frequency that it must be regarded as a characteristic feature of the disease.[16] Other evidences of general, severe disturbances in nutrition and vitamin deficiency may be recognized elsewhere in the body — for example, in the skeleton, in the wasting, hypertrophy of muscles, in the disappearance of fat from the fat depots and in the general retardation of growth. Keratinizing metaplasia in the upper respiratory tract, pancreas, salivary glands or renal pelvis, characteristic of vitamin A deficiency, is occasionally but not regularly found.[14, 16]

Etiology

Pancreatic achylia may be caused by congenital atresia or stenosis of the pancreatic ducts, or congenital malformation of the duodenum and head of the pancreas.[14, 16] Congenital syphilis causing widespread fibrosis of the pancreas or intrauterine infection of unknown etiology producing obliteration to the duct system may well be responsible in some cases. In the majority of cases, however, the pancreatic achylia is unassociated with any such gross congenital anomalies or inflammatory lesions obstructing the outflow of pancreatic juice.[16] To clarify the pathogenesis of the lesion producing pancreatic achylia in this large group of infants and children, three causes have been suggested; namely, vitamin A deficiency, a filterable-virus infection and a fundamental alteration in the physical character of the acinar secretion.

A deficiency of vitamin A may be responsible for gross obstruction of the pancreatic ducts,[14] but this is a rare event.[16] Following metaplasia of the epithelium of the duct lining to a stratified squamous type, there may be complete filling of the ducts by masses of desquamated, keratinized epithelial cells. Some evidence of vitamin A deficiency on histologic examination of certain organs, not necessarily including the pancreas, was found by Andersen[14] in 23 per cent of the cases studied or collected. In our own experience,[16] evidences of vitamin A deficiency were less frequent than this. Although there is a defect in the absorption of vitamin A associated with this pancreatic disease, it must now be regarded as merely one of the complications of the disease process, not of primary importance in the pathogenesis of the pancreatic lesion but responsible for some of the symptoms and laboratory findings.[16]

The frequent occurrence of chronic bronchopneumonia in infants with pancreatic disease of this type and the finding of inclusion bodies in certain cases have justified further investigation of the possible role of a filterable virus in the etiology of this condition. Brody[21] has recently reported the finding of inclusion bodies in 2 of 3 patients with pancreatic fibrosis. Experimental support for this suggestion is still lacking. A review carried out with the assistance of Dr. Edward Pratt[22] of 50 post-mortem examinations of infants who suffered from a severe degree of this pancreatic disease disclosed intranuclear and cytoplasmic inclusions in the salivary glands, lungs, trachea or pancreas in 6 (12 per cent) of the series. This is no greater than the incidence of cytoplasmic and intranuclear inclusion bodies in the total number of autopsies in the same laboratory.[23] These studies, therefore, provide no support for the suggestion that a virus disease is of primary importance in the causation of this pancreatic lesion, although secondary effects from a possible superimposed virus infection cannot be excluded.

The prominence of the inspissated secretions in the pancreas in this disease suggested to Blackfan and Wolbach[24] in 1933 that this striking lesion could be attributed to the production of an abnormal pancreatic secretion. Study of 87 cases of the advanced lesion and about 350 cases of early stages of the process support the hypothesis that the basic lesion consists in a physically altered pancreatic secretion, which causes intrinsic obstruction in the acini and small ducts, finally leading to dilatation and obstruction in the larger ducts.[16, 20] Atrophy

of the acinar structures follows, and condensation of the connective-tissue framework of the pancreas secondary to loss of parenchyma, combined with an ingrowth of new fibrosis tissue, gives the picture of diffuse fibrosis. Support for this theory comes from the observation that the fully developed clinical picture of the celiac syndrome may exist and the pancreatic enzymes in the duodenal contents may be markedly reduced at a time when the sole lesion in the pancreas consists of inspissation of secretion in the acini and small ducts, with no evidence of atrophy of the parenchyma, fibrosis or dilatation of the large ducts.[25] Further evidence of the abnormality of the pancreatic secretion is given by the gross appearance of the scanty, extremely thick and viscid pancreatic juice obtained when the duodenal contents are collected for enzyme analysis, as contrasted with the thin, watery pancreatic juice obtained from normal infants or from those suffering from true idiopathic celiac disease.[25]

Inspissation of secretions and dilatation of glandular structures of the same general character as these alterations in the acini and small ducts of the pancreas are found at autopsy on these patients in the glands of the trachea, bronchi, esophagus, duodenum, gall bladder and intestinal tract. Inspissation of bile to a degree sufficient at times to cause intrahepatic biliary obstruction may also occur. These findings suggest that the inspissation of altered secretions in the pancreatic acini is only a part of a generalized disorder of secretory mechanisms involving many glandular structures but exerting its greatest effect on the pancreas.[16] In experiments on kittens, suggested by this conception of the pathogenesis of the pancreatic lesion, it has been possible to produce, by the administration of parasympatheticomimetic drugs (pilocarpine and Mecholyl), the histologic picture of inspissation of secretions in the acini and small ducts in the pancreas and the clinical picture of a severe chronic nutritional disturbance.[16] The cause for this suggested disturbance of the secretory mechanism in the pancreatic acini of infants remains to be demonstrated.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**
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CASE 29421

PRESENTATION OF CASE

A forty-one-year-old night watchman was admitted to the hospital because of intermittent gas pains of ten years' duration.

The patient was apparently well until about ten years prior to entry, when he developed intermittent attacks of indigestion in which he suffered from epigastric gas pains and the sensation that his stomach was "tied up in knots." The pain occurred approximately half an hour after eating, or when he had gone three or more hours without eating, and lasted for about an hour. It was relieved by anything that would "break the gas" and produce gaseous eructations, such as soda, milk or food. The attacks were sometimes precipitated by cabbage, pork and fried foods. Vomiting of undigested food, especially fried food, sometimes gave relief. The vomitus was never bloody, nor did it contain coffee-grounds material. The last attack of vomiting occurred six weeks before admission. Three years before admission, following x-ray examination at a community hospital, he was placed on a strict ulcer regime, with prompt symptomatic relief as well as gain in weight. The diet, however, was discontinued six months later and the symptoms recurred. Nine months prior to entry, while working in a dusty atmosphere, he had two or three attacks of vomiting and his symptoms increased in severity for two months, at which time he obtained another job, with some relief in his condition. In the three or four months before entry he experienced daily distress after almost every meal. There was anorexia and a weight loss of 15 pounds. He subsisted mainly on soups, milk and cream, crackers, tea and so forth. He became progressively weaker.

He had been constipated most of his life and had habitually taken various laxatives. There had been no back pain, heartburn, dizziness or fainting. He smoked one package of cigarettes daily and drank some beer and a little whisky. He had experienced considerable financial difficulties.

Physical examination showed a well-developed, small, wiry, tense man, with evidence of recent weight loss. There was no pallor. He was edentulous. The tongue was reddened and coated with coarse papillae. The heart and lungs were normal. The abdomen was scaphoid and soft. There was no tenderness, spasm or palpable masses. Peristalsis was active. Rectal examination revealed a small, firm, nontender prostate. Considerable tenderness was elicited superiorly and on the left, where a questionable soft mass was palpated.

The blood pressure was 125 systolic, 80 diastolic. The temperature was 98.6°F., the pulse 76, and the respirations 20.

The blood showed a red-cell count of 4,300,000, with a hemoglobin of 14 gm. The white-cell count was 6800, with 63 per cent neutrophils. The urine was normal. The stools were guaiac negative on eight occasions but gave a ++++ test on one occasion. The blood Hinton test was negative. The nonprotein nitrogen was 20 mg. per 100 cc. The blood protein was 5.6 gm. per 100 cc., the carbon dioxide combining power 21 millimols per liter, the chloride 95.9 milliequiv. per liter and the blood sugar 74 mg. per 100 cc. Gastric analysis showed no free acid before and half an hour after histamine injection; the values for total acidity were 5 and 18 units respectively. Both aspirations gave a ++ guaiac test.

X-ray examination showed a normal esophagus. Just below the cardia there was an ulcer crater measuring 1 by 1 cm., with a rigid, soft-tissue mass surrounding it. This filling defect measured 4 cm. in length. The remainder of the stomach and duodenum was normal.

The patient was placed on a gastric diet with tincture of belladonna, 15 drops, and phenobarbital, 2 gr., three times a day. His condition improved. Gastroscopic examination eight days after entry showed a normal antrum and pylorus and an increased reddening of the body of the stomach in the upper part, with a few streaks of bright-red blood. There was a marked verrucous, cobblestone appearance in the upper 4 or 5 cm. near the cardia; no ulcer crater could be demonstrated. Following gastroscopy, the epigastric symptoms recurred but were relieved by Creamalin, 45 cc. every two hours. A gastric analysis on the fifteenth day showed 25 units of free acid and a total acid of 35 units half an hour after histamine injection. X-ray examination after one month on the medical regime showed the ulcer crater to be smaller than it was formerly, but the crater was surrounded by what appeared to be a polypoid mass extending along the lesser curvature for about 8 cm. The lesser curvature was rigid in this area.

An abdominal exploration was performed six days later.

*On leave of absence.

Differential Diagnosis

Dr. William B. Breed: It seems to me that there are two possibilities to be considered. Either this lesion was a benign one throughout its course or it started as a peptic ulcer, then degenerated and became malignant. The history certainly is suggestive of the latter supposition. You will note that the early story is indicative of peptic ulcer with periodic pyloric obstruction and relief of symptoms on an ulcer regime, as well as recurrence of symptoms when the regime was discontinued.

The dusty atmosphere of his new job can be disregarded. I have no thoughts about that.

Two or three months prior to entry he began to have continual discomfort directly after eating, with anorexia and loss of weight but no typical symptoms of ulcer. Up to that point this could well have been a benign ulcer near the cardia that had degenerated and had become malignant. Gastroscopy possibly confirmed the nature of the process: the upper part of the stomach wall was verrucous and cobblestone in appearance.

Dr. Edward B. Benedict: That does not mean malignant disease. That means gastritis.

Dr. Breed: I am glad you are here, Dr. Benedict. The record states, "a marked verrucous, cobblestone appearance." There was no mass? Will you describe it as you remember it?

Dr. Benedict: A verrucous and cobblestone appearance may mean chronic hypertrophic gastritis

Dr. Breed: In a localized area?

Dr. Benedict: Sometimes localized, sometimes generalized. This was fairly well localized.

Dr. Breed: You introduce the idea here at once that this lesion was benign. Let us go ahead and see whether we can put that together with the second examination by x-ray, which described a polypoid mass extending along the lesser curvature, with a rigid mucosa.

In passing, I should say that one has to consider lymphoma of the stomach in any condition like this. However, I am willing to conclude that if this was a polypoid mass it probably was not due to lymphoma. Do you ever see polyps in lymphoma, Dr. Benedict?

Dr. Benedict: Not discrete polyps.

Dr. Breed: You saw no polypoid mass?

Dr. Benedict: No, but I could not see the ulcer. It was in a part of the stomach that is difficult to visualize.

Dr. Breed: No polyp was seen on the first x-ray examination. We might see both sets of film.

Dr. Milford Schulz: Here are the films made at the time of admission, and there is no gainsaying the fact that there is an ulcer with what appears to be a mass of soft tissue about it. In addition you can see an irregular soft-tissue mass extending into the cardia.

Dr. Breed: What does that mean to you? Is this soft-tissue infiltration?

Dr. Schulz: By all the rules it should be a carcinoma.

Here are the films made after a month of treatment. The ulcer is somewhat smaller. You still see all this thickened verrucous soft tissue extending into the air-filled and barium-filled portion of the stomach. It is true that there are quite prominent mucosal folds throughout the stomach; in a recent similar case, however, in which a diagnosis of cancer was made, the condition at operation proved to be gastritis and not carcinoma.

Dr. Breed: This is not that case by any chance?

Dr. Schulz: No.

Dr. Breed: Kindly show me the polyp.

Dr. Schulz: There is no true polyp, but there are numerous soft-tissue masses extending into the gas bubble of the stomach and displacing the barium. Here is the defect in the stomach in which the ulcer lay. By all the rules that should be a neoplasm.

Dr. Breed: I am going to stick to the rules, because it is a fairly straightforward history and I see no reason for trying to be too smart. The patient had an ulcer for ten years and then developed a cancer at the site of the ulcer.

Dr. Benjamin Castleman: Is there any other comment?

Dr. J. H. Means: I think it could be a leiomyoma. I am not offering that as one of the possibilities, but it seems to me that I recall that they are apt to run a more or less benign course for some years and then become increasingly malignant.

Dr. Castleman: They usually give a long history of bleeding and become larger extremely slowly. A few of them do become malignant, however.

Dr. Means: What about other tumors of the stomach, such as fibroma?

Dr. Castleman: I do not believe that an accurate differential diagnosis of the various intramural tumors — fibroma, neurofibroma and leiomyoma — can be made clinically or by x-ray, or even microscopically in some cases.

Dr. Means: I discussed that point with Dr. George W. Holmes some years ago. He claimed that when they were smooth and round it was one thing, and when lobulated it was another. How about the significance of these differences? Does the lobulation mean anything?

Dr. Castleman: A definite lobulation is perhaps more in favor of a neurofibroma, but all these

tumors tend to be well circumscribed and round. They often have a central ulceration.

DR. SCHULZ: An intramural tumor is usually quite characteristic in appearance roentgenologically. It displaces or smooths out the mucosa rather than showing soft-tissue masses extending into the lumen of the stomach.

DR. BREED: I shall have to add that he had gastritis as well as cancer.

DR. BENEDICT: I think the ten-year history is in favor of a benign lesion.

DR. BREED: Such as?

DR. BENEDICT: Benign ulcer. Of course that brings up the question, Do benign ulcers ever become malignant? A lot of people think that they never do.

DR. CASTLEMAN: I was about to take issue with Dr. Breed's statement.

DR. BREED: I have two against me.

DR. CASTLEMAN: We are certain that an ulcer remains an ulcer and does not degenerate into a carcinoma. I believe that there are a few cases with definite ulceration in the stomach, proved roentgenologically, that ten years later develop carcinoma in the same location — that is, in the ulcer. If one checks some of these histories of long-standing ulcer with carcinomatous degeneration one often discovers that the ulcer was in the duodenum and not in the stomach, and things of that sort. It is true that carcinoma can remain in the precancerous state, — carcinoma in situ, — limited to the mucosa, without invasion over a long period of time. We have seen several examples of this condition.* Furthermore, precancerous lesions have been known to exist for six or seven years in the cervix. These carcinomas in situ may ulcerate; they are, however, ulcerating carcinomas, rather than carcinomas developing in benign ulcers.

DR. BREED: Along that line, it did occur to me when I was studying this case that the patient might have had a duodenal ulcer and that this was a new malignant lesion. I am willing to go back to that idea. Since the pathologist insists that ulcers do not degenerate, I shall probably have to agree; but I still think that the lesion was malignant.

DR. MEANS: The picture could fit with carcinoma in situ, could it not?

DR. CASTLEMAN: It could, although ten years is a long time for carcinoma in situ; most of them are under five years in duration.

DR. RONALD C. SNIFFEN: This area of the stomach is rather unusual for carcinoma in situ, is it not?

*Mallory, T. B. Carcinoma in situ of stomach and its bearing on histogenesis of malignant ulcers. *Arch. Path.* 30:348-362, 1940.

DR. CASTLEMAN: Yes; most of the lesions have been in the prepyloric region.

DR. BREED: The patient may have had a duodenal ulcer for ten years and then developed cancer of the stomach in the cardia. I am willing to accept that.

CLINICAL DIAGNOSIS

Carcinoma of stomach.

DR. BREED'S DIAGNOSES

Carcinoma of stomach.
Duodenal ulcer?
Chronic gastritis.

ANATOMICAL DIAGNOSIS

Acute and chronic phlegmonous gastritis, with gastric erosions and ulcerations.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The surgeon's operative notes state that he was able to feel two ulcers, one close to the cardia and one 5 or 6 cm. below that. He thought that the lesion was probably benign, but since he was not absolutely sure, and since the ulcers were high in the cardia, he believed that the patient would do better by having a resection.

When the stomach was opened, we found innumerable ulcers. Some were old, measuring 2 or 3 mm. in diameter, with a greenish-fibrinoid base, the result of necrosis. Between the ulcers the mucosa was markedly edematous and red and the rugae were prominent. This appearance reminded me of that of ulcerative colitis, with bridges between the ulcers. It might be called a phlegmonous gastritis.

Microscopic sections showed an acute and chronic inflammatory reaction throughout the whole wall, with necrosis of the mucosa and the formation of erosions and deep ulcers. We were unable to find a chronic ulcer that the patient might have had for ten years. It may have been in the duodenum, or the more recent disease may have covered it.

DR. BENEDICT: Were they true peptic ulcers, or erosions?

DR. CASTLEMAN: Both were present.

DR. BENEDICT: How do you distinguish between them?

DR. CASTLEMAN: One speaks of an erosion if the destruction extends to the muscularis mucosa; if it goes beyond that, it is an ulcer. The etiology is the same.

There was no evidence of malignant disease.

CASE 29422

Presentation of Case

A fifty-four-year-old press operator entered the hospital because of uterine prolapse.

The patient had been in good health all her life. She had had four pregnancies, only two of which terminated successfully. About eight years before admission she was told by her physician that she had prolapse. About the same time she developed increased frequency and occasional slight incontinence. There was no nocturia. About one year before entry she noted protrusion of a mass between her legs. At first the mass appeared after prolonged standing and on coughing or exertion. The prolapse increased in amount and she developed low abdominal pain, slightly increased urinary frequency and occasional slight incontinence. There was nocturia (one to three times). She had lost 30 pounds during the year before entry.

Physical examination showed an obese woman in no distress. The fundic vessels were tortuous, and there was moderate arteriovenous nicking. The lungs were clear. The heart was normal. The sounds were regular and of good quality. The liver edge was palpated two fingerbreadths below the costal margin. There was an "enormous" rectocele, with an ulcer on the posterior vaginal wall near the cervix and another on the cervix. A large cystocele was also present. The fundus of the uterus was not particularly enlarged; it was palpated almost at the level of the introitus.

The blood pressure was 184 systolic, 110 diastolic. The temperature was 99.2°F., the pulse 88 and the respirations 20.

Examination of the blood showed a hemoglobin of 90 per cent and a white-cell count of 12,250. Urinalysis revealed a ++ test for albumin; the sediment contained 3 white cells per high-power field. The blood Hinton test was negative. A urine culture was negative. A vaginal culture showed colon bacilli, *Staphylococcus aureus* and beta-hemolytic streptococci.

On the third hospital day a vaginal hysterectomy and perineorrhaphy were performed under ether and nitrous oxide anesthesia. During the course of the operation, which lasted three hours, the blood pressure fell to 80 systolic, 40 diastolic, with a rise of pulse to 100. With intravenous fluids, however, the pressure gradually rose to 100 systolic, 70 diastolic, at which level it remained the last hour of the operation. At the end of the operation she was given 500 cc. each of plasma and blood, with a subsequent rise of systolic blood pressure to 220.

Following operation, the patient failed to regain consciousness or even respond to painful stimuli. Examination revealed absence of motion in any part of the body. The neck was not stiff. The abdomen and heart were not "too remarkable." There was no upward motion of the eyes, which remained fixed, looking straight ahead. The pupils were dilated, measuring 4 mm. in diameter. They were round and regular but failed to react to light. The face was flat, flabby, symmetrical and motionless. The tongue moved when stimulated. The muscles of the extremities were symmetrical. A slight increased resistance to passive stretch was noted in the right leg. There were no adventitious movements. No reaction to pinpricks could be elicited. The biceps, triceps, radial, knee and ankle reflexes were "very lively," with increased knee jerks on the right. Bilateral ankle clonus and Babinski reflexes were present, and there was an increased Hoffmann sign on the right. The nonprotein nitrogen was 18 mg. per cent, and the chloride 100.3 milliequiv. per liter.

The patient remained unconscious, and died twenty hours after operation.

Differential Diagnosis

Dr. Julia G. Arrowood: This discussion should answer two questions: By what accident or mechanism did this catastrophe occur? Was it possible to foresee and prevent it? Since at these meetings we desire to arrive at the final diagnosis as a sort of climax, let us first examine the somewhat meager information we have in search of an answer to the second question.

The patient was obese, arteriosclerotic and hypertensive. The cardiac examination is disposed of in two sentences. "The heart was normal. The sounds were regular and of good quality." With a diastolic pressure of 110, I should be inclined to expect some cardiac enlargement and hypertrophy. It is stated that she had nocturia. How did the quantity of day and night urine compare?

Dr. Benjamin Castleman: There is no further statement in the record.

Dr. Arrowood: Was there a cardiac consultation or an electrocardiogram?

Dr. Castleman: No.

Dr. Arrowood: The temperature of 99.2°F. and the white-cell count of 12,250 can be explained by the ulcerated condition of the large cystocele and rectocele. It would be interesting, however, to know if she had a daily elevation of temperature during the preoperative hospital stay.

Dr. Castleman: The temperature on admission was 99.2°F. It fell to normal the following day and remained so during the entire preoperative period.

Dr. Arrowood: Whether or not this death could have been foreseen and prevented, one can

only say that patients of this type are notoriously poor risks, and that their cardiac status should be carefully investigated before surgery is undertaken.

It is obvious that during the operative period this woman must have had an episode of cerebral anoxia, which resulted in complete functional decerebration. The persistent coma, with absent superficial reflexes, hyperactive deep reflexes and the presence of bilateral ankle clonus and Babinski reflexes, indicates widespread cerebral damage. It seems likely that this may have occurred in one of three ways: from asphyxia following overdosage of the anesthetic agent, from respiratory obstruction or from a cerebrovascular accident during the operation.

There is no mention of any untoward happening, but I would like some additional information about the course of anesthesia. Was the induction satisfactory? Was there cyanosis, obstruction or respiratory difficulty at any time? What was the anesthetist's estimate of the anesthesia and of the patient's condition at its close? I assume, however, that there was no period of acute respiratory failure to account for the patient's condition.

The second possibility is that the cerebral damage was produced by hypoxia lasting over a considerable period of time. The lithotomy position in an obese patient causes considerable embarrassment to respiration by pressure of the abdominal contents against the diaphragm. The operation lasted three hours, and the blood pressure fell to 80 systolic, 40 diastolic. In this connection, I should like to know what the initial blood-pressure reading on the anesthesia sheet is, and when the fall occurred. It is stated, "The pressure gradually rose to 100 systolic, 70 diastolic, at which level it remained the last hour of the operation." What was the blood pressure on the patient's return to the ward, and how long was it before it reached a more nearly normal level—say 130 systolic, 80 diastolic? My point is that hypoxia from respiratory embarrassment due to position, combined with a blood pressure that was very low for this patient, whose blood-pressure reading on the ward was 184 systolic, 110 diastolic, might have been sufficient to produce the fatal brain damage.

The third possibility is that the patient had a cerebrovascular accident during the time of anesthesia and operation. This could have been a massive hemorrhage with continued bleeding, reaching proportions sufficient to cause the extensive damage that occurred. It is quite conceivable that there had been previous coronary disease with cardiac infarction and mural thrombosis and such a cardiac thrombus could have been the origin of a cerebral embolus, which in turn formed the basis for a growing thrombus. Finally it is possible that during the long period of hypotension in this arteriosclerotic patient, a thrombus could have originated in a cerebral vessel, the early signs being masked by the anesthesia.

To be specific concerning my diagnosis, I do not believe that the patient had any episode of acute anoxia to account for her death, but that she had a cerebrovascular accident, either thrombosis, hemorrhage or embolus. I do not believe it is possible to differentiate these with the evidence we have, but my guess is in the order named.

DR. CASTLEMAN: Dr. Brenizer, you saw this patient during operation. Will you tell us about the case?

DR. A. G. BRENIZER: The patient had good color throughout the operation. There was no cyanosis or anything like that, just a drop in blood pressure uncontrolled by intravenous fluids.

DR. RICHARD H. SWEET: Was the intravenous solution running before or after the fall in blood pressure had occurred?

DR. BRENIZER: It was started as soon as we were notified that the blood pressure was falling. The 5 per cent dextrose and physiologic saline solution was changed over to plasma as soon as possible.

DR. SWEET: Was there much loss of blood?

DR. BRENIZER: I should say moderate.

DR. SWEET: There is apt to be with that type of operation.

DR. CHARLES S. KUBIK: Was there anything else to indicate that something had happened suddenly? Was the drop in blood pressure rapid?

DR. BRENIZER: The drop in blood pressure was rather sudden.

DR. FREDERIC B. MAYO: In answer to Dr. Arrowood's question concerning neurologic opinion, three diagnoses were considered: thrombosis at the time that the blood pressure dropped; hemorrhage when the blood pressure rose so high; and cerebral anoxia, which was subsequently ruled out by information that anesthesia was uneventful.

DR. SWEET: One of the conditions that I fear most in practicing surgery is the marked drop in pressure from ether or nitrous oxide anesthesia in a person who has or may have cardiovascular disease, especially those with hypertension. This patient probably had hypertension, and the fall to the level that she reached is, in itself, enough to explain the things that happened to her. The possibility that such an accident may occur is one reason why many of us do not use spinal anesthesia in patients of that sort.

DR. JACOB LERMAN: Sudden rise in systolic blood pressure from a low level to 220 suggests a rapid increase in intracranial pressure. That would per-

haps fit more with subarachnoid than with cerebral hemorrhage.

Clinical Diagnosis

Cerebral anoxia.

Dr. Arrowood's Diagnosis

Cerebrovascular accident (thrombosis, hemorrhage or embolus).

Anatomical Diagnoses

Cerebral embolus, left middle cerebral artery.
Cerebral infarction with temporal pressure cone.
Subacute bacterial endocarditis, mitral valve.
Chronic rheumatic endocarditis, with stenosis of mitral valve.

Pathological Discussion

Dr. Castleman: At autopsy this patient showed a cerebral embolus, which Dr. Kubik will describe. The heart was moderately enlarged, weighing 370 gm. There was a marked degree of mitral stenosis, on which was superimposed a subacute bacterial endocarditis that must have been present long before operation. A thrombus had undoubtedly broken off and entered the brain.

Dr. Charles S. Kubik: The embolus was in the left middle cerebral artery, and infarction of a large portion of the left cerebral hemisphere corresponding to the distribution of the occluded artery had occurred. An unusual feature was marked swelling of the left hemisphere, with herniation of the hippocampal gyrus into the notch of the tentorium and resulting compression of the midbrain. The aqueduct was flattened, and there were small hemorrhages in the midbrain. The herniation, or temporal pressure cone, through its effect on the midbrain unquestionably accounted for the dilated fixed pupils and for the bilateral extensor plantar responses and was probably responsible to a large degree for the deep state of coma and eventual fatal outcome.

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FOREIGN RELIEF AND REHABILITATION

War can leave little but disaster in its wake, and it is to offset its miseries so far as possible and as quickly as possible that the Office of Foreign Relief and Rehabilitation Operations was organized. This organization, under the directorship of former Governor Lehman, of New York, has recently reported on activities of the medical personnel attached to its North African mission, and described its preparations for medical and sanitary measures in future relief theaters.

In North Africa, public-health officers assigned to OFRRO by the U. S. Public Health Service have been working with the North African relief and rehabilitation mission for the past six months, gaining valuable experience in medical relief. They have been attached by General Eisenhower to the military command, in charge of activities affecting civilian health, and they work through the French civil authorities, utilizing existing health and governmental services and professional personnel.

Acting in a military capacity, members of the OFRRO serve practically as public-health officers of the Army. Thus, medical personnel of the mission entered Tunis within twenty-four hours after the city's fall, establishing sanitary controls for the region, and the same was done in the Pantelleria and Lampedusa campaigns.

Among the varied duties of the medical personnel of OFRRO have been assisting the French authorities in obtaining lend-lease medical supplies, helping to restore normal health service in cities and rural districts, advising in the creation of modern health departments, as was done at Oran, establishing de-lousing stations to check the spread of typhus, and disinsecticizing airplanes to prevent the spread of insect-borne disease.

Meanwhile, in order that future relief programs in distant theaters may be expeditiously carried out, different types of standard packaged units of medical supplies are being assembled in the United States for immediate shipment to any area. Thus, one basic unit containing the minimal medical supplies required for the control of the more frequent diseases of world-wide occurrence is designed to meet the needs of a group of 100,000 people for a one-month period, and includes some one hundred and fifty items. A larger unit, containing approximately fifteen hundred items, is planned to care for a group of 1,000,000 people for a three-month period. Supplemental packages are designed to combat epidemic disease, or conditions peculiar to certain regions.

In addition, standard hospital units have been prepared. One includes the essential equipment

for a 50-bed hospital, and another that for a 150-bed hospital. Laboratory units contain equipment for an epidemic-control laboratory, an emergency field laboratory, a laboratory for a 50-bed or a 150-bed hospital, a central pathological laboratory and a laboratory supply center. A few public-health teams are also being recruited, a typical team being made up of a health officer, a sanitary engineer, a pediatrician, a medical nutritionist, a medical supply officer, a nursing specialist, a malariologist, if necessary, and a hospital nutritionist.

Our nation, more power to it, has always been eager to spread its good works abroad. In the excitement of rebuilding the Eastern Hemisphere, however, we must not lose sight of our own problems that are just causes for anxiety and concern. In eventually putting our own house in order we must accept the challenge of a rising venereal-disease rate; we must cope with an influx of tropical diseases; we must face, far more intelligently and humanely than we have yet done, the problem of rehabilitation of many thousands of young men rejected by their draft boards or discharged from the army as unfit for further military service; and, last but not least, we must provide some means, other than that proposed by Senators Wagner and Murray, for improving the health of the people of the Nation.

SHOCK THERAPY

The brilliant results obtained by the use of plasma and plasma substitutes in shock are well known and occupy an important place in modern war surgery. But investigators have not limited their observations to this one therapeutic method.

The question whether to warm or cool the patient in shock has recently received considerable attention. First-aid courses continue to teach that the application of external heat is a cardinal principle in the treatment of shock—indeed it is practically the only method of therapy (except leaving the patient alone) that may be practiced by the first-aid worker; and it is often assumed that a patient cannot be overheated so long as his skin is not burned by hot applications. Yet all current reports that bear on the subject clearly indicate that the overzealous application of heat is harmful in shock. This is equally true whether it is due to burns,[1] trauma or hemorrhage.[2] Indeed, a little thought along physiologic lines makes this obvious. Shock is a state in which the circulating blood volume is inadequate, with resulting anoxia. The local application of heat produces cutaneous vasodilatation, and this, in turn, causes the blood volume to become even more inadequate, owing to the greater vascular bed; furthermore, an increase in tissue metabolism resulting from warming the whole body increases the anoxia, and sweating augments dehydration. It therefore seems unwise to use hot-water bottles, heating pads and other sources of external heat to such an extent that the internal temperature of the body is raised above normal levels. As a matter of fact, induced hyperthermia may reproduce the shock syndrome.

As a corollary, it might be supposed that cooling of the body would be beneficial. However, two experimental studies[1, 2] have shown that this may also be inadvisable, although not quite so dangerous as overheating. In experimental burns in rats, the optimal environmental temperature range for survival seems to lie between 75 and 95°F.[1] Local refrigeration of an injured extremity may, on the other hand, be beneficial if ice is applied to the extremity during a prolonged crush[3] or during the prolonged application of a tourniquet.[4] It is obvious that more studies are required to determine the true value of local refrigeration in traumatic shock.

Stern,[5] from Russia, offers evidence that secondary shock is benefited by the intracisternal injection of a solution of potassium phosphate. She claims that the potassium stimulates the sympathetic centers and that the phosphate by reducing the concentration of ionized calcium, depresses parasympathetic tone. Since sympathomimetic drugs are generally understood to be ineffective or harmful in shock, confirmation of this observation, especially with reference to the ultimate rates of survival, is desirable.

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MEDICAL EPONYM

Heerfordt's Syndrome

In an article entitled "Über eine 'Febris uveoparotidea subchronica,' an der Glandula parotis und der Uvea des Auges lokalisiert und häufig mit Paresen cerebrospinaler Nerven kompliziert [Febris Uveoparotidea Subchronica, Localized in the Parotid Gland and the Uvea of the Eye, and Frequently Complicated by Pareses of the Cerebrospinal Nerves]," in Albrecht von Graefes *Archiv für Ophthalmologie* (70: 254-273, 1909), Dr. C. F. Heerfordt reports three cases. A portion of the translation follows:

> The cases reported by me, together with that of Daireaux-Pechin and von Collomb's case constitute a clinically well-defined disease group with such peculiar characteristics that it would seem quite proper to establish them — for the present — as a special disease entity — a "febris uveoparotidea subchronica" — that is different from acute epidemic parotid fever.
>
> We consider the following to be characteristic of this febris uveoparotidea subchronica: the protracted course of the illness, the prolonged low-grade fever, the localizations in the parotid gland and the uvea of the eye and, in addition, the frequent occurrence of complicating pareses of the cerebrospinal nerves. Finally, in my observation, this disease entity seems to be only mildly infectious.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

ATWOOD — Charles A. Atwood, M.D., of Taunton, died October 10. He was in his eighty-third year.

Dr. Atwood received his degree from Harvard Medical School in 1883. He was a member of the staff of the Morton Hospital and a consultant of the Taunton State Hospital. He had been medical examiner in the First Bristol District many years. He was a member of the Massachusetts Medical Society and the American Medical Association.

A brother survives.

CORRESPONDENCE

DEPRIVATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held October 6, the Board voted to revoke the license of Dr. Theodore Rosen, 9A Summit Avenue, Brookline, because of gross misconduct in the practice of his profession as shown by his conviction in court.

H. Quimby Gallupe, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

BOOK REVIEW

Transurethral Prostatectomy. By Reed M. Nesbit, M.D. 4°, cloth, 192 pp., with 62 plates. Springfield, Illinois: Charles C Thomas, 1943. $7.50.

This monograph is timely and fills the need for an orderly description of transurethral resection. The material is arranged in four sections.

The first consists of ten chapters, which present the mechanics and principles of prostatic resection and comprise the most significant contribution of this monograph. Practical clinical information can be obtained from these clearly and well-written chapters. The excellent drawings by Mr. Didusch simplify and co-ordinate the various steps in the procedure.

The New England urologist will be interested in the second section (Chapter XI), which is an enthusiastic appraisal of the author's management of prostatism by transurethral surgery. The conservative resectionist who limits and selects his patients for transurethral surgery will note that this is a method not only for prostatic resection but also for transurethral prostatectomy, since the author does not hesitate to operate on glands yielding 100 to 150 gm. of tissue. He will read with envy and amazement that the technic offers the following advantages — freedom from postoperative discomfort and sepsis, bed confinement only for the day of operation, no postoperative strictures or urinary incontinence and a mortality rate as low as 1.2 per cent. Over a decade has passed since the introduction of the present methods of transurethral resection. With the comparative safety of modern surgery, the morbidity of a technic is almost as important as the mortality. This chapter occupies but 10 pages and, in the opinion of the reviewer, is entirely inadequate. It would be more convincing if a detailed and faithful follow-up study, including postoperative urologic and roentgenologic examinations, were a part of this chapter. Many urologists have subsequently operated on patients who had had transurethral surgery done by prominent resectionists, and it is surprising that such failures do not appear in the end-result statistics. It seems as though it were time for a definite evaluation of this procedure to be made.

The third section (Chapter XII) deals with the history of transurethral prostatic resection. It makes interesting reading and is well illustrated. The fourth is composed of a well-selected bibliography, grouped alphabetically according to the authors' names and also classified according to pertinent subdivisions.

This monograph is instructive but the reviewer does not believe that it will be instrumental in converting the conservative urologist to the author's point of view.

(Notices on page xii)